American Journal of Hematology 56:12–16 (1997)

Heparin-Induced Thrombocytopenia With Thrombosis: Incidence, Analysis of Risk Factors, and Clinical Outcomes in 108 Consecutive Patients Treated at a Single Institution

Sucha Nand,* Warren Wong, Benjamin Yuen, Andrew Yetter, Edwin Schmulbach, and Susan Gross Fisher

Section of Hematology/Oncology, Department of Medicine, Loyola University of Chicago and Loyola University Cancer Center, Maywood, Illinois

Heparin-induced thrombocytopenia with thrombosis (HITT) can lead to serious morbidity and may be potentially fatal. We reviewed our experience with this entity over a 4-year period, to determine the following: 1) incidence and type of thrombosis in patients with heparin-induced thrombocytopenia (HIT), 2) clinical consequences of thrombosis, i.e., amputation, cerebrovascular accidents and death, 3) risk factors associated with development of thrombosis, and 4) impact of therapy on clinical outcomes in patients with HITT. Between 1991–1994, 108 patients were diagnosed to have HIT by heparin-induced platelet aggregation test. Thirty-two (29%) of these developed thrombotic complications, of which 20 were venous, 8 arterial, and 4 both. Five of the 32 died, 3 underwent amputations, and 3 had cerebrovascular accidents. The patients who developed thrombotic complications, when compared to those with HIT alone, were older (68.7 ± 11.5 vs. 63.3 ± 16 years, $P = .05$), had more severe thrombocytopenia (platelet count 46,300 ± 30,400/mm^3 vs. 62,500 ± 34,400/mm^3, $P = .02$), and developed it earlier (6.0 ± 2.9 vs. 7.4 ± 3.1 days, $P = .03$). Multivariate analysis showed that severity of thrombocytopenia and early fall in platelet count were independent risk factors for development of thrombotic complications. We did not find an association between development of thrombosis and clinical events (myocardial infarction, cardiac procedures or surgery, noncardiac surgery, and sepsis) that occurred immediately prior to onset of thrombocytopenia. Heparin was stopped in all 32 patients with HITT. Six received no additional therapy, and one received a single dose of aspirin. Three of these 7 died. The other 25 received anticoagulant or multiagent therapy, with 2 deaths. The death rate was lower in those who were treated with anticoagulant or multiagent therapy ($P = .05$). We conclude that: 1) Thrombotic complications occur in about 29% of hospitalized patients who develop HIT. 2) Early, severe fall in platelet count in elderly patients receiving heparin appears to be associated with development of thrombotic complications. 3) Our data do not show an association between development of thrombotic complications and clinical events immediately preceding the diagnosis of HIT. 4) In addition to discontinuation of heparin, anticoagulant or thrombolytic therapy should be considered in patients with HITT. Am. J. Hematol. 56:12–16, 1997.

Key words: heparin; thrombocytopenia; thrombosis

INTRODUCTION

About 5% (range 0–30%) of patients receiving unfractionated heparin develop heparin-induced thrombocytopenia (HIT), and about 10% of those (0.5% of the entire group) develop thrombosis (HITT), which can involve the arterial, the venous, or both systems [1–6]. Patients may develop cerebrovascular accidents, myocardial infarction, limb ischemia, deep venous thrombosis, and, rarely, ischemia of other organs. The thrombotic complications are fatal in about 29% of patients, and an additional 21% have to undergo limb amputations [1]. Hep-

*Correspondence to: Sucha Nand, M.D., Section of Hematology/Oncology, Department of Medicine, Loyola University of Chicago and Loyola University Cancer Center, 2160 So. First Ave., Maywood, IL 60153.

Received for publication 13 September 1996; Accepted 7 May 1997.

arin-induced thrombocytopenia is mediated through immune mechanisms, in which heparin acts as a hapten [7–13]. Recently it has been demonstrated that the antibody produced is against heparin-platelet factor 4 complex [14–16]. Platelet factor 4 (PF4) is a heparin-binding protein found in alpha granules of platelets and is released upon platelet activation. The antibody against the heparin-PF4 complex is mostly IgG, but may be IgM. Some investigators have divided HIT into two clinical subtypes [3]. In subtype I, the thrombocytopenia is mild (platelet count usually above 100,000/mm^3), and presumably results from in vivo platelet aggregation. The patients remain asymptomatic, and platelet count may return to normal even with continuation of heparin therapy. In subtype II, thrombocytopenia is severe, the platelets are also activated, and thromboembolic complications may be seen.

Why some patients with HIT develop thrombotic complications is not clear. It has been shown that the antibodies are reactive against the endothelial surface [17], which has glycosaminoglycans, which are heparin-like substances that can bind to platelet factor 4. This may predispose to endothelial injury and thrombosis. In some patients with HIT, the levels of protein C (PRC), antithrombin III (AT-III), and heparin cofactor fall during the thrombocytopenic period, suggesting a global activation of the coagulation cascade [18]. The thrombotic complications in patients with HIT are not associated with the presence of malignancy, or incidental deficiency of AT-III, PRC, or protein S (PRS) [18]. Surgery preceding HIT appears to be associated with venous thrombosis. If patients develop cardiovascular events or complications, they have a significant risk of developing arterial thrombosis [18].

We undertook this retrospective study to determine the incidence of thrombosis in patients with HIT and to identify the clinical risk factors associated with its development. We present data on 108 consecutive patients seen at our institution between 1991–1994, and we examine the association between thrombotic complications and clinical parameters like preexisting illnesses and concomitant events. We also examine the outcomes, and effect of therapy on morbidity and mortality.

MATERIALS AND METHODS

Medical records of all patients with thrombocytopenia and a positive heparin-induced platelet aggregation test (HIPA) seen at our institution between January 1991–December 1994 were reviewed. This test, based on reports by Ansell and Deykin [9], Rhodes et al. [19], and Fratantoni et al. [20], was done as follows: control and patient are run simultaneously, and 0.220 ml of heat-inactivated control or patient serum are mixed with 0.140 ml of donor platelet-poor plasma. These specimens are placed in a Sienco Platelet Aggregometer (Sienco Inc., Morrison, CO) set at 100% light transmittance. Another set of samples is prepared as above, but with platelet-rich plasma instead of platelet-poor plasma. These are placed in the aggregometer at 0% light transmittance, and .040 ml of 0.9% NaCl are then added to control and patient samples. The specimens are mixed and incubated at 37°C for 15 min and checked for spontaneous aggregation. If no spontaneous aggregation is detected, .040 ml of an aggregating agent (epinephrine, Adenosine Diphosphate, or collagen) are added to each cuvette to verify the viability of platelets. If spontaneous aggregation is detected, heparsorb procedure is employed to remove heparin. Another set of samples is prepared to be tested on a second Sienco Platelet Aggregator (0.220 ml of heat-inactivated control or patient serum are mixed with 0.140 ml donor platelet-poor plasma, and the aggregometer is set to 100% light transmittance; 0.220 ml of heat-inactivated control or patient serum are mixed with 0.140 ml donor platelet-rich plasma (PRP), and the aggregometer is set to 0% light transmittance). When the 0% light transmittance remains steady, .040 ml of stock heparin (10 units/ml) are added into each cuvette (control or patient serum + PRP + heparin). The specimens are allowed to mix and incubate at 37°C for 15 min while charting the percent light transmittance. After 15 min, .040 ml of epinephrine or another aggregating agent (ADP or collagen) are added to any test cuvette which does not show aggregation, to verify the viability of platelets. A negative result was defined as absence of aggregation of donor platelets in patient serum upon addition of exogenous heparin. A positive result was defined as aggregation of donor platelets in patient serum in the presence of, but not in the absence of, heparin.

The medical records were reviewed to obtain data on age, sex, admitting diagnosis, history of smoking, ethanol use, past or family history of thrombosis, medications on admission, peripheral pulse examination, details of heparin therapy received by the patient (type, route, dose, and duration), initial date of thrombocytopenia, date of HIPA positivity, development of thrombosis, and major clinical events (myocardial infarction, angioplasty, surgery, sepsis, disseminated intravascular coagulation, or any other) immediately preceding HIPA positivity and thrombotic complications. Thrombocytopenia was defined as a platelet count of <150,000/mm^3. In postoperative periods after coronary artery bypass or cardiac valvular surgery, the thrombocytopenia must have been present for 2 days, and the thrombocytopenic period was counted from the second day.

Data were analyzed using parametric techniques. Comparisons between outcome groups (thrombosis vs. no thrombosis) were made based on Student's t-test and the chi-square test for continuous and categorical variables, respectively. In the case of categorical variables

TABLE I. Clinical Characteristics of Patients With Heparin-Induced Thrombocytopenia (HIT) and Heparin-Induced Thrombocytopenia With Thrombosis (HITT)

	HIT	HITT
Total number of patients	76	32
Male:female	38:38	14:18
Age (mean)	68.7 ± 11.5	63.3 ± 16.0 ($P = .05$)
Positive family history of thrombosis	0	1
Positive past history of thrombosis	1	0
Major clinical event before development of HAT or HATT		
Cardiac events[a]	38	20
Noncardiac surgery	25	8
Sepsis	2	1
Miscellaneous[b]	11	3
Lowest platelet count ($\times 1{,}000/mm^3$)	62.5 ± 34.5	46.4 ± 30.4 ($P = .02$)
Time to develop thrombocytopenia (days)	7.4 ± 3.1	6.0 ± 2.9 ($P = .03$)

[a]Cardiac events include angina, myocardial infarction, coronary angioplasty, coronary artery bypass grafting, and valvular surgery.
[b]Miscellaneous events include trauma, carcinoma of the stomach, carcinoma of the prostate, cirrhosis of liver, renal failure, and scleroderma.

with very small cell frequencies, Fisher's exact test was calculated. Multiple logistic regression was used to identify independent predictors of outcome. A two-sided alpha level of 0.05 was considered statistically significant for all tests.

RESULTS

A total of 108 patients was diagnosed to have HIT during the study period. The median age was 68 years, and 56 of the patients were females. One patient had a prior history of venous thrombosis, one had a positive family history of thrombosis, and 60 had previous history of heart disease. Twenty-two patients gave a history of smoking. Before the development of HIT, 58 patients had a cardiac event or surgery (angina, myocardial infarction, angioplasty, coronary artery bypass surgery, or valvular surgery), 33 had noncardiac surgery, 3 had sepsis, and 14 had miscellaneous medical problems (trauma, gastric cancer, prostate cancer, cirrhosis of the liver, renal failure, hypertension, scleroderma, or subarachnoid hemorrhage) (Table I). Eight patients received heparin by subcutaneous route, 15 received only intravenous flushes, and the rest received intravenous infusions.

A total of 32 patients (29%) developed thromboembolic complications. Of these, 20 were venous (14 had deep venous thrombosis with or without pulmonary embolism, and 6 had pulmonary emboli without apparent deep venous thrombosis), 8 were arterial (5 ischemia of extremities, 2 Cerebrovascular accidents (CVA), and one myocardial infarction due to thrombosis of bypass grafts), and 4 were both (limb ischemia, Deep venous thrombosis (DVT), and PE in 3 patients; limb ischemia, PE, and CVA in one). Five patients out of these 32 died (2 with PE, 2 with gangrenous changes involving extremities, and one with limb ischemia and PE) (Table II).

TABLE II. Thrombotic and Fatal Complications Seen in Patients With Heparin-Induced Thrombocytopenia and Thrombosis (HITT)*

Thrombotic complications	Number
Arterial	
Limb ischemia	5 (2 deaths)
Myocardial infarction	1
Cerebrovascular	2
Total	8
Venous	
DVT	10
DVT and PE	4 (1 death)
PE without apparent DVT	6 (1 death)
Total	20
Both arterial and venous	
DVT, PE, limb ischemia	3 (1 death)
PE, cerebrovascular	1
Total	4

*DVT, deep venous thrombosis; PE, pulmonary embolism.

TABLE III. Treatment of Heparin-Induced Thrombocytopenia With Thrombosis (HITT) and Its Outcome

Treatment	No. of patients	Amputations	Deaths	Recoveries
1. Discontinuation of heparin	6	0	2	4
2. Discontinuation of heparin + aspirin[a]	1	0	1	0
3. Discontinuation of heparin + coumadin	8	0	2	6
4. Discontinuation of heparin + dextran-40	2	1	0	1
5. Discontinuation of heparin + multiple agents[b]	15	2	0	13

[a]Received a single dose (325 mg) of aspirin.
[b]Use of two or more agents. These included coumadin + dextran-40 (5 patients), coumadin + aspirin (2 patients), dextran + aspirin (1 patient), coumadin + dextran + aspirin (5 patients), hirulog + dextran-40 + coumadin (1 patient), and streptokinase + dextran + coumadin (1 patient).

Heparin was stopped in all patients who developed HITT. Six patients received no additional therapy, and 2 of these died. One patient received a single dose of aspirin (325 mg), but he also expired. Eight were treated with additional coumadin, with 2 deaths in this group. Two patients received dextran-40. There were no deaths, but one had to undergo a limb amputation. Fifteen patients received more than one agent (dextran-40, aspirin, thrombolytic therapy, hirulog, or ancrod), with 6 of these developing PE and 2 requiring limb amputation. There were no deaths in this group (Table III).

Comparison between those who had HIT alone with those who developed thrombotic complications showed the following differences: 1) Patients who developed

thrombotic complications tended to be older (68.7 ± 11.5 years) than those who did not (63.3 ± 16) ($P = .05$). 2) There was a significant difference between groups in the platelet count at diagnosis. In patients who developed HITT, it was 46,400 ± 30,400/mm^3, as compared to 62,500 ± 34,5000/mm^3 ($P = .02$) in those who developed only HIT. 3) Time to development of thrombocytopenia was shorter (6.0 ± 2.9 vs. 7.4 ± 3.1 days, $P = .03$) in those who developed HITT vs. those who developed HIT alone. In multivariate analysis, both 1 and 2 were independent predictors of thrombosis.

There were 3 deaths (3/7 = 42%) among those in whom heparin was discontinued and in whom either no additional treatment was given or aspirin alone was administered. There were 2 deaths in 25 patients who received alternate anticoagulant therapy or multiagent treatment. This difference reached statistical significance (Fisher's exact test, $P = .05$).

DISCUSSION

Heparin-induced thrombocytopenia remains a relatively frequent side effect of a commonly used medication. Though the thrombocytopenia in itself is harmless as a rule, the subset of patients who develop thrombotic complications suffer grave consequences. Thrombotic complications prove fatal in about 30% of patients, and lead to amputation or residual disability in about 20%. The underlying mechanisms for HIT are better understood at present, but the pathophysiology of HITT remains obscure.

Even though Green et al. [7] had shown in 1978 that the heparin-platelet complex acts as an antigenic determinant which induces HIT, the platelet proteins involved in this process were not known till 1994. That year, many groups made the key observation that it is platelet factor 4 that binds with heparin in the causation of HIT [14–16,21]. Amiral et al. [22] recently reported that some patients with HIT have autoantibodies to interleukin-8 and neutrophil-activating peptide-2. However, why some patients with HIT develop HITT remains unclear. In vitro studies suggest that sera from some patients with HIT contain antibodies that react with heparin bound to the endothelial surface or with heparan sulfate synthesized by the endothelial cells. This may lead to immune-type injury to the endothelium [17]. The size of the heparin molecule may be important in the causation of HITT. Recently, a randomized, double-blind trial of low molecular weight heparin (LMWH) vs. unfractionated heparin as prophylactic therapy in 665 patients after hip surgery revealed that none of the patients receiving LMWH developed thrombocytopenia [23,24]. Low molecular weight heparin is less efficient in activating platelets (hence a less effective release of platelet factor 4) [25], and binds less avidly to platelet factor 4 [26], when compared to unfractionated heparin. On the other hand, LMWH has been shown by others to induce HIT [27,28]. A study of clinical and laboratory characteristics of 53 patients with HIT, 36 of whom developed HITT, revealed that there was global activation of the coagulation cascade (fall in protein C, antithrombin-III, and heparin cofactor-II) during the thrombocytopenic period [18]. There were significant associations between concomitant cardiovascular events (including myocardial infarction and cardiovascular surgery) and arterial thrombosis, and surgery of any type and the development of venous thrombosis.

We have used the platelet aggregation method to diagnose HIT at our institution since 1981. The sensitivity of this method has been reported to be between 70–88%, and specificity between 82–100% [1,3]. Others have reported that the serotonin release assay may be more sensitive and specific than the platelet aggregation test [29]. We believe that our long experience with the platelet aggregation test was helpful, even though we might have underestimated the true incidence of HIT in our patient population. Our study included all inpatients between January 1, 1991–December 31, 1994 who tested positive by this method (those suspected of HIT with a negative heparin-induced platelet aggregation were not included). This gave us a cohort of patients seen at a tertiary-care center who are at risk of developing HITT. About 29% of patients who had HIT developed thrombotic complications. This may be an overestimate because of the referral patterns, the relative insensitivity of the HIPA test, and the fact that some patients were transferred to us after the diagnosis had been suspected. Our data indicate that patients who develop HITT tend to be older, and they develop a more severe thrombocytopenia than those with HIT alone. Thrombocytopenia also tends to appear early in those who develop thrombosis. Cardiac events and surgery did not appear to influence the risk of thrombosis.

It is not clear why older patients with early and severe (subtype II) HIT tend to develop thrombotic complications. It is possible that endothelial damage may result from a stronger immune reaction to heparin-platelet factor 4 complex, triggering thrombosis. The elderly patient may be more prone to thrombosis because of preexisting vascular abnormalities. Obviously, further information is necessary to explain the development of thrombosis in patients with HIT.

Most investigators consider stopping heparin as the single most important step in the treatment of HITT. Numerous treatments, which include antiplatelet agents, anticoagulants, thrombolytic therapy, hirulog, heparan sulfate, ancrod, synthetic antithrombins, and surgical interventions have been tried in patients with HITT [30–37]. However, there are no studies that show if therapy influences the final outcome. Our data suggest that discontinuation of heparin may not be sufficient in patients with HITT. One patient was given a single aspirin. We do not consider this a therapeutic intervention and include

this patient in the group in whom heparin withdrawal was the sole intervention (Table III). Patients who received an anticoagulant, or more than one type of treatment (antiplatelet agents, anticoagulants, hirulog, ancrod, or thrombolytic therapy), had a smaller risk of death when compared to those in whom heparin was stopped and aspirin was the only therapy utilized. Our numbers are not large enough to indicate any differences in the amputation rates.

Despite the limitations of our study, we believe that it brings out new and clinically relevant information. In a tertiary-care patient population, studied in a consistent manner, the risk of developing thrombosis in patients with heparin-associated thrombocytopenia is about 29%. We are able to identify certain risk factors that are associated with the development of the risk of thrombosis. We also suggest more aggressive treatment of HITT, as it may decrease the risk of death in these patients.

REFERENCES

1. King DJ, Kelton JG: Heparin associated thrombocytopenia. Ann Intern Med 100:535–540, 1984.
2. Warkentin TE, Kelton JG: Heparin-induced thrombocytopenia. Prog Hemost Thromb 10:1–34, 1991.
3. Chong BH: Heparin-induced thrombocytopenia. Br J Haematol 89: 431–439, 1995.
4. Schmitt BP, Adelman B: Heparin associated thrombocytopenia: A critical review and a pooled analysis. Am J Med Sci 305:208–215, 1993.
5. Chong BH, Berndt MC: Heparin induced thrombocytopenia. Blut 58: 53–57, 1989.
6. Chong BH: Heparin induced thrombocytopenia. Blood Rev 2:108–114, 1988.
7. Green D, Harris K, Reynolds N, Roberts M, Patterson R: Heparin immune thrombocytopenia: Evidence for a heparin-platelet complex as the antigenic determinant. J Lab Clin Med 91:167–175, 1978.
8. Trowbridge AA, Caraveo J, Green JB, Amaral B, Stone MJ: Heparin-related immune thrombocytopenia. Studies of antibody-heparin specificity. Am J Med 65:227–283, 1978.
9. Ansell J, Deykin D: Heparin induced thrombocytopenia and recurrent thrombocytopenia. Am J Hematol 8:325–332, 1988.
10. Cines DB, Kaywin P, Bina M, Tomaski A, Schreiber AD: Heparin associated thrombocytopenia. N Engl J Med 303:788–795, 1980.
11. Chong BH, Ismail F: The mechanism of heparin induced platelet aggregation. Eur J Haematol 43:245–251, 1989.
12. Kelton JG, Sheridan D, Santos A, Smith J, Steeves K, Smith C, Brown C, Murphy WG: Heparin-induced thrombocytopenia: Laboratory studies. Blood 72:925–930, 1988.
13. Warkentin TE, Kelton JG: Heparin induced thrombocytopenia. Annu Rev Med 40:31–44, 1989.
14. Visentin GP, Ford SE, Scott JP, Aster RH: Antibodies from patients with heparin-induced thrombocytopenia thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. J Clin Invest 93:81–88, 1994.
15. Greinacher A, Potzsch B, Amiral J, Dummel V, Eichner A, Mueller-Echhardt C: Heparin-associated thrombocytopenia: Isolation of the antibody and characterization of the multimolecular PF4-heparin complex as the major antigen. Thromb Haemost 71:247–251, 1994.
16. Kelton JG, Smith JW, Warkentin TE, Hayward CP, Denomme GA, Horsewood P: Immunoglobulin G from patients with heparin-induced thrombocytopenia binds to a complex of heparin and platelet factor 4. Blood 83:3232–3239, 1994.
17. Cines DB, Tomaski A, Tannenbaum S: Immune endothelial cell injury in heparin-associated thrombocytopenia. N Engl J Med 316:581–589, 1986.
18. Boshkov LK, Warkentin TE, Hayward C, Andrew M, Kelton JG: Heparin induced thrombocytopenia and thrombosis. Clinical and laboratory studies. Br J Haematol 84:322–328, 1993.
19. Rhodes GR, Dixon RH, Silver D: Heparin-induced thrombocytopenia with thrombotic and hemorrhagic manifestations. Surg Gynecol Obstet 136:409–413, 1973.
20. Fratantoni JC, Pallet R, Gralnick HR: Heparin-induced thrombocytopenia: Confirmation of diagnosis with in vitro methods. Blood 45:395–401, 1975.
21. Amiral J, Bridey F, Wolf M, Boyer-Neumann C, Fressinaud E, Vissac AM, Peynaud-Debayle E, Dreyfus M, Meyer D: Antibodies to macromolecular platelet factor 4-heparin complexes in heparin induced thrombocytopenia. A study of 44 cases. Thromb Haemost 73:21–28, 1995.
22. Amiral J, Marfaing-Koka A, Wolf M, Alessi MC, Tardy B, Boyer-Neumann C, Vissac AM, Fressinaud E, Poncz M, Meyer D: Presence of autoantibodies to interleukin-2 or neutrophil-activating peptide-2 in patients with heparin associated thrombocytopenia. Blood 88:410–416, 1996.
23. Warkentin TE, Levine MN, Hirsch J, Horsewood P, Roberts RS, Gent M, Kelton JG: Heparin induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 332:1330–1335, 1995.
24. Aster RH: Heparin-induced thrombocytopenia and thrombosis [editorial]. N Engl J Med 332:1374–1376, 1995.
25. Barradas MA, Mikhalidis DP, Epemolu O, Jeremy JY, Fonseca V, Dandona P: Comparison of the platelet pro-aggregatory effect of conventional unfractionated heparins and a low molecular weight heparin fraction (CY222). Br J Haematol 67:451–455, 1987.
26. Lane DA, Pejler G, Flynn AM, Thompson EA, Lindahl U: Neutralization of heparin-related saccharides by histidine rich glycoprotein and platelet factor 4. J Biol Chem 261:3980–3985, 1986.
27. Eichinger S, Kyrle PA, Brenner B, Wagner B, Kapiotis S, Lechner K, Kominger HC: Thrombocytopenia associated with low-molecular-weight heparin. Lancet 1:1425–1427, 1991.
28. Leroy J, Lerclerc MH, Delahousse B, Huerois C, Goloppe P, Gruel Y, Touelemonde F: Treatment of heparin-associated thrombocytopenia and thrombosis with low-molecular-weight heparin (CY216). Semin Thromb Hemost 11:326–329, 1985.
29. Sheridan D, Carter C, Kelton JG: A diagnostic test for heparin-induced thrombocytopenia. Blood 67:27–30, 1986.
30. Matsuo T, Yamada T, Chikahara Y, Kadowaki S: Effect of aspirin on heparin-induced thrombocytopenia in a patient requiring hemodialysis. Blut 59:393–395, 1989.
31. Mehta DP, Yoder EL, Appel J, Bergsman KL: Heparin-induced thrombocytopenia and thrombosis: Reversal with streptokinase. Am J Hematol 36:275–279, 1991.
32. Magnani HN: Heparin-associated thrombocytopenia. An overview of 230 patients treated with Orgaran (Org 10172). Thromb Haemost 70: 554–561, 1993.
33. Matsuo T, Kario K, Chikahira Y, Nakao K, Yamada T: Treatment of heparin-induced thrombocytopenia by use of argatroban, a synthetic thrombin inhibitor. Br J Haematol 82:627–629, 1992.
34. Demers S, Ginsburg JS, Brill-Edwards P, Panju A, Warkentin TE, Anderson DR, Turner C, Kelton JG: Rapid anticoagulation using ancrod for heparin-induced thrombocytopenia. Blood 78:2194–2197, 1991.
35. Nand S, Robinson JA: Plasmapheresis in the management of heparin-associated thrombocytopenia with thrombosis. Am J Hematol 28:204–206, 1988.
36. Nand S: Hirudin therapy for heparin-associated thrombocytopenia and deep vein thrombosis. Am J Hematol 43:310–311, 1993.
37. Chong BH, Ismail F, Cade J, Gallus AS, Gordon S, Chesterman C: Heparin-induced thrombocytopenia: Studies with a new low-molecular-weight heparinoid, Org 10172. Blood 73:1592–1596, 1989.